

## **REMARKS**

This Amendment is presented in response to the Office Action dated March 14, 2011.

### **Status of Claims**

Claims 38, 39, 43-55, 58, 60-65, and 68 –72 and 74 are now pending in this application. Independent claims 38 and 69 have been amended to clarify that the method of treatment is limited to the **acute** treatment of conditions such as migraine, without prejudice to seeking broader coverage in a continuation application. Claims 57 and 73 have been cancelled. No fees are due.

### **Claim Rejections – 35 U.S.C. §112**

In the Office Action, the Examiner rejected claim 57 under 35 U.S.C. §112, second paragraph. Claim 57 has now been cancelled, rendering this rejection moot. Independent claims 38 and 69 have been amended. Support for language relating to acute treatment is found in the specification, e.g., at paragraph [0039]. Support for the time period of “from about 15 to about 30 minutes” is found, e.g., from cancelled claim 73.

### **Claim Rejections – 35 U.S.C. §103**

In the Office Action, the Examiner rejected claims 38, 45-52, 57, 58, 65, 68, 73 and 74 under 35 U.S.C. §103(a) as being unpatentable over Franz et al. GB 2098865 A in view of Saper et al. (2002, Headache, Volume 42, pages 470-482) and Drizen et al. U.S. Patent No. 5,897,880.

The Examiner’s rejection is respectfully traversed.

Franz is directed to a topical pharmaceutical composition in the form of a microemulsion incorporating a skin-penetrable active agent. The active agent may be tizanidine, although the microemulsions are said to be indicated for the systemic administration “of any active agent.” Page 4, lines 22-35. Franz does not hint or suggest that its formulations should be applied “onto the skin of a human patient at the posterior cervical area in close proximity to the brain stem” as required by the present claims. Indeed, Franz is not directed to a method of treatment at all, but rather to the skin penetration of active agents.

To the extent that Franz directs one of ordinary skill in the art at all, it would lead one away from the claimed method. In fact, at page 5, lines 46 – 54, Franz discusses permeation of human abdominal skin, and at page 6 lines 23-24, tizanidine was applied behind the ear.

Saper et al. describes a clinical study in which all patients treated with tizanidine were treated with tizanidine tablets orally to assess the efficacy of tizanidine as adjunctive *prophylactic therapy* for chronic daily headache (chronic migraine, migrainous headache, or tension-type headache). In contrast to the presently claimed invention, Saper et al. seek to use tizanidine as adjunctive prophylactic therapy, *not as a rapid treatment of a condition which is occurring at the time of treatment (acute treatment)*.

In order to further clarify this difference, independent claim 38 has been further amended to call for the treatment to be applied to a human patient experiencing “*an acute condition*” selected from the group consisting of migraine, cluster headache, muscle sprain, muscle spasm, spasticity, tension headache and tension related migraine... such that the unit dose provides a therapeutic effect *within about 15 to about 30 minutes* after topical administration to the human patient.” Thus, the presently claimed method is for acute treatment, whereas Saper et al. describes prophylactic therapy. *These situations are not the same, nor does Saper et al. hint or suggest that (oral) tizanidine can be used, either alone or together with other active agents, to treat acute conditions.*

The Examiner relies on Drizen et al. as “teaching topical gelled compositions to be administered topically and transdermally through the skin into various sites where the drug is therapeutically effective (abstract and column 3 lines 30-35).” The Examiner further relies on the examples in Drizen et al. for support that Drizen teaches treatment to the posterior cervical area in close proximity to the brain stem with respect to its NSAID formulations.

However, Drizen et al. describes a topical formulation in which a drug is entrapped in a polymer matrix “such that when it is administered, it is *slowly released into the systemic circulatory system or muscular tissue* providing a method of delivering an active drug to an affected site in the body through the skin.” Column 3, lines 31-46. That is quite different from the presently claimed invention, where the drug is not being administered to an affected site or into the systemic circulatory system. Rather, the tizanidine (and optional additional serotonin agonist/ergot alkaloid) is administered to the Cervico-Trigeminal Complex via the skin at the back of the neck, which is not intended to provide significant systemic blood levels of the drug(s), and in fact the dose may be subtherapeutic if administered via its traditional route. (See, e.g., claim 51). This mechanism is explained in detail in the Declaration of Inventor Dr. Ronald Aung-Din which was previously submitted on December 10, 2010 (see, e.g., pages 8-11).

In fact, in each and every example of Drizen, et al., the slow release formulation of Diclofenac – a drug which is in a different class than tizanidine – is applied directly to the site of the patient’s pain, which in some cases included the neck region. It is quite a jump from a description of a topical treatment of Diclofenac at an affected site to achieve a slow release and systemic and local effect to a treatment of an immediate release drug in a different classification (NSAID versus skeletal muscle relaxant) to act at the neuro-transmitter sites on the free nerve-endings, the effect of which is then transmitted by neural impulse propagation as afferent input to the cervical spinal cord, brainstem, and other CNS structures where the clinical benefit is achieved. (See, e.g., page 10 of the Aung-Din Declaration).

It is respectfully submitted that this jump that is being taken by the Examiner is not an obvious one. It would not be obvious to use a different drug in a completely different type of formulation (immediate release providing an immediate effect, versus a slow release and repeated administration 2-3 times per day (see the Drizen examples) to provide an effect) for a completely different purpose (direct treatment of CNS structures via the Cervico-Trigeminal Complex in the claimed invention, versus localized treatment of muscular tissue or systemic treatment). Drizen et al. provide no suggestion that their formulation could be modified to provide an immediate release, rapidly acting formulation for acute treatments. In fact, Drizen et al. specifically state that the "molar ratio of the polymers present in the matrix is critical in this invention." Column 3, lines 46-47. Drizen et al. state that any deviation from that molar ratio diminishes the potency and efficacy. Column 3, lines 51-58. Contrary to the Examiner's position on page 12 of the Office Action, Drizen et al. does not provide relief in "essentially the same way" and would not achieve the same results. The Examiner has no basis for that position given the fact that Drizen et al. critically require the use of a slow release polymer system.

Further, it is respectfully submitted that the Examiner has not considered the unexpected results which are explained in the Declaration of Inventor Aung-Din, submitted on December 10, 2010. It is respectfully submitted that the evidence of unexpected results overcomes any prima facie obviousness position set forth by the Examiner. Once again, it appears that the Examiner has not considered the unexpected results submitted by the inventor, as comments by the Examiner with respect to the patentability of claim 74 reflect: "Thus in the absence of secondary considerations, such as unexpected results, claims 74 of the instant application is rendered obvious." Office Action dated March 14, 2011 at page 13, lines 1-2.

Accordingly, it is respectfully submitted that the Examiner's rejection on this basis has been overcome and should be removed.

The Examiner also rejected claims 39, 60-64 and 69-72 under 35 U.S.C. 103(a) as being unpatentable over Franz et al, in view of Saper et al. and Drizen et al. and further in view

of Aung-Din et al. Aung-Din et al. is specifically cited for teaching sumatriptan for the treatment of migraines. Aung-Din does not hint or suggest that tizanidine can be useful, either together with a serotonin agonist or alone, in acute treatment of migraine. Nor does Aung-Din hint or suggest any beneficial effects of any other drugs other than a serotonin agonist being administered at the posterior cervical region of a human patient. It is respectfully submitted that the combination of prior art relied upon by the Examiner still does not render the invention obvious, for reasons explained in detail above. Applicant has also demonstrated the benefits of treatment of serotonin agonists via administration of the same at the posterior cervical region of a patient for the acute treatment of migraine, as set forth, e.g., in the previously mentioned Declaration of Inventor Aung-Din, submitted on December 10, 2010.

Accordingly, it is respectfully submitted that the Examiner's rejection on this basis has been overcome and should be removed.

The Examiner further rejected claims 53-55 and 64 under 35 U.S.C. 103(a) as being unpatentable over Franz et al, in view of Saper et al. and Drizen et al. and further in view of Plachetka. Plachetka is specifically cited for teaching dihydroergotamine for the treatment of migraines. Accordingly, it is respectfully submitted that the combination of prior art relied upon by the Examiner still does not render the invention obvious, for reasons explained in detail above.

Accordingly, it is respectfully submitted that the Examiner's rejection on this basis has been overcome and should be removed.

In the Office Action, the Examiner rejected claims 38, 45-52, 57, 58, 65, 68, 73 and 74 under 35 U.S.C. 103(a) as being unpatentable over Murdock et al. U.S. Publication No. 2002/0015713 in view of Saper et al. and Drizen et al. The Examiner took the position that Murdock et al. teach a transdermal composition for the treatment of pain in a subject comprising a skeletal muscle relaxant in a pharmaceutically acceptable carrier, and further specifically

teaches a composition containing amine compounds having biphasic solubility such as adrenergic agonist compounds for the treatment of pain, wherein the preferred adrenergic agonist compound is tizanidine, citing paragraph [0041] of Murdock et al. (See Office Action at page 17).

To the extent that Murdock et al. describes a transdermal formulation which may include tizanidine as an active agent, it is respectfully submitted that the Murdock et al. reference is cumulative to Franz et al. The Examiner then goes further and takes the position that “Murdock et al. further teaches that topical application of a pain-relieving composition to the neck resulted in complete and rapid resolution of migraine like headache [0144]. Thus Murdock et al. teaches a method of treating migraine pain comprising the application of a topical pain-relieving composition to the neck of a patient.” (Office Action, page 18).

The Examiner's rejection is respectfully traversed.

Murdock et al. describe a transdermal composition for the treatment of pain in a subject, which includes an amine containing compound having biphasic solubility, which term is specifically defined in paragraph [0026] of Murdock as “compounds having at least one amine moiety and having sufficient lipid solubility...***such that the compound passes through the stratum corneum, and has sufficient aqueous solubility to be active in the aqueous environment of the dermis and the underlying tissue.***” In fact, Example 62 of Murdock et al. (paragraph [0144] cited by the Examiner describes a treatment of a 24 year old woman with a history of 3 back surgeries and cervical degenerative disc disease. A composition containing carbamazepine and gabapentin was applied to her neck, her arms and her wrist. The composition thus contained two anticonvulsant drugs, carbamazepine and gabapentin (see paragraph [0122]. Both of these drugs may be used to treat nerve related pain (neuropathic pain); however, neither is in the class of a muscle relaxant.

It is respectfully submitted that Murdock et al., and in particular Example 62, is describing local treatment of areas which are painful to the patient – the neck, arms and wrist, and has no hint or suggestion that the application of a muscle relaxant to the Cervico-Trigeminal Complex via the skin at the back of the neck would provide acute treatment of migraine, cluster headache, muscle sprain, muscle spasm, spasticity, tension headache and tension related migraine. It is further respectfully submitted that in making this rejection, the Examiner has not considered the unexpected results set forth in the Declaration of Inventor Dr. Ronald Aung-Din which was previously submitted on December 10, 2010.

It is further respectfully submitted that the Saper and Drizen references relied on in combination with Murdock et al. do not overcome the deficiencies of Murdock et al. for the reasons previously explained above, as well as for other reasons.

Accordingly, it is respectfully submitted that the Examiner's rejection on this basis has been overcome and should be removed.

In the Office Action, the Examiner also rejected claims 39, 60-64 and 69-72 under 35 U.S.C. 103(a) as being unpatentable over Murdock et al, in view of Saper et al. and Drizen et al. and further in view of Aung-Din et al. Aung-Din et al. is specifically cited for teaching sumatriptan for the treatment of migraines. Aung-Din does not hint or suggest that tizanidine can be useful, either together with a serotonin agonist or alone, in acute treatment of migraine. Nor does Aung-Din hint or suggest any beneficial effects of any other drugs other than a serotonin agonist being administered at the posterior cervical region of a human patient. It is respectfully submitted that the combination of prior art relied upon by the Examiner still does not render the invention obvious, for reasons explained in detail above. Applicant has also demonstrated the benefits of treatment of serotonin agonists via administration of the same at the posterior cervical region of a patient for the acute treatment of migraine, as set forth, e.g., in the previously mentioned Declaration of Inventor Aung-Din, submitted on December 10, 2010.

Accordingly, it is respectfully submitted that the Examiner's rejection on this basis has been overcome and should be removed.

The Examiner further rejected claims 53-55 and 64 under 35 U.S.C. 103(a) as being unpatentable over Murdock et al, in view of Saper et al. and Drizen et al. and further in view of Plachetka. Plachetka is specifically cited for teaching dihydroergotamine for the treatment of migraines. Accordingly, it is respectfully submitted that the combination of prior art relied upon by the Examiner still does not render the invention obvious, for reasons explained in detail above.

Accordingly, it is respectfully submitted that the Examiner's rejection on this basis has been overcome and should be removed.

### **Double Patenting**

In the Office Action, the Examiner rejected claims 38, 39, 45-52, 57, 58, 60-65 and 68-74 for obviousness-type double patenting as being unpatentable over claims 2-21 of copending Application No. 123/460,966 in view of Saper et al.

It is respectfully requested that this rejection be held in abeyance until an indication of allowability of claims is received.

### **Conclusion**

It is respectfully submitted that there is nothing within the prior art suggesting the administration of a skeletal muscle relaxant such as tizanidine at the posterior cervical region of a patient for the acute treatment of "experiencing a condition selected from the group consisting of migraine, cluster headache, muscle sprain, muscle spasm, spasticity, tension headache and tension related migraine... such that the unit dose provides a therapeutic effect within about 15

to about 30 minutes after topical administration to the human patient.” In this regard, the Applicant has demonstrated the benefits of treatment (rapid onset of therapeutic effect) at the posterior cervical region of human patients with respect to tizanidine (see Examples 1 -5). The Examiner’s attention is further directed to the fact that the claims reflect the fact that the patient is experiencing, e.g., migraine at the time of treatment, and that the treatment provides a rapid therapeutic effect, and that the Examiner has apparently not considered the unexpected results set forth in the previously submitted Declaration of Inventor Dr. Ronald Aung-Din.

The Examiner is invited to contact the undersigned by telephone if it is determined that any further issues remain.

A favorable action on the merits is respectfully requested.

Respectfully submitted,

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